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ORIGINAL

Efficacy of targeting high mean arterial pressure for older patients with septic shock (OPTPRESS): a multicentre, pragmatic, open-label, randomised controlled trial

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Abstract

Purpose: We examined the effect of a high-target mean arterial pressure (MAP) on septic shock in a previously underrepresented region.

Methods: A multicentre, pragmatic, open-label, randomised controlled trial was conducted in 29 hospitals in Japan, where the prevalence of chronic hypertension among older individuals is 66.9%. Patients who were diagnosed with septic shock, aged ≥ 65 years, and admitted to an intensive care unit were randomised 1:1 to the high (target MAP = 80–85 mmHg) or control (target MAP = 65–70 mmHg) groups from 1 July 2021 to 12 December 2023. The target MAP was maintained for 72 h or until vasopressors were no longer required. The primary outcome was the 90-day all-cause mortality. Secondary outcomes included organ support-free days and adverse events.

Results: The trial was terminated early on the basis of the interim analysis results, suggesting the harm of the high-target strategy. Of the 518 patients, 258 were in the high-target group, and 260 were in the control group. By 90 days after randomisation, 101 patients (39.3%) in the high-target group and 74 (28.6%) in the control group had died from any cause (risk difference = 10.7; 95% confidence interval, 2.6–18.9). Renal replacement therapy-free days at 28 days were shorter in the high-target group. No clinical benefits for any outcome were observed in any subpopulation, including those with known chronic hypertension.

Conclusion: Among older patients with septic shock, high-target MAP significantly increased mortality compared with standard care.

Trial registration: UMIN Clinical Trials Registry; UMIN000041775; 13 September 2020.

Keywords: Clinical trial, Critical care, Emergency medicine, Geriatrics, Septic shock

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Introduction

Sepsis is a major health care challenge worldwide. Septic shock is a subset of sepsis with a high mortality rate of approximately 38.5% even in developed countries [1]; it is characterised by sustained hypotension despite adequate fluid infusion [2] and requires immediate stabilisation of patient haemodynamics. However, the optimal target blood pressure, a key factor in circulatory management for septic shock, remains debatable [3].

Recent randomised trials in Europe and North America showed that a target MAP of > 65 mmHg in vasodilatory shock is not always beneficial [4–7]. However, targeting an MAP of 80–85 mmHg was suggested to benefit septic shock patients with chronic hypertension in some studies [8–10]. A previous trial [6] suggested that a lower target MAP of 60–65 mmHg is preferable in older patients; fewer than half of the participants in the trial had septic shock, and subgroup analysis reported that the effect of target blood pressure varied by disease [6]. Since autoregulation controlling organ perfusion varies depending on patient demographics, disease type, and severity [11, 12], the effect of the target MAP requires further examination in the population that has not been examined in previous trials regarding race, disease specificity, or prevalence of chronic hypertension. Additionally, since the results of previous trials might have been affected by catecholamine-related adverse events, the effect of a high-target MAP should be examined using a protocol minimising catecholamine dosage.

Therefore, we conducted a randomised trial evaluating the effects of high-target MAP, using a protocol of early concomitant use of vasopressin, in patients with septic shock aged ≥ 65 years in Japan in those the reported prevalence of chronic hypertension was 66.9%, according to a national survey [13].

Methods

Study design

The Optimal Target Blood Pressure in Elderly with Septic Shock (OPTPRESS) trial was a multicentre, pragmatic, open-label, randomised controlled trial conducted at 29 Japanese centres. Patients aged ≥ 65 years with septic shock were screened and randomised. Written informed consent was obtained from all the patients or their relatives. In cases of emergency, the trial procedures were applied, and informed consent was obtained subsequently. The trial protocol was published elsewhere [14]. This trial was pre-registered to the UMIN-Clinical Trials Registry (UMIN000041775).

Take-home message

Targeting a MAP of 80–85 mmHg increased the 90-day mortality, compared to usual care, among 518 Japanese patients with septic shock aged ≥ 65 years. While this RCT targeted a population with a 66.9% prevalence of chronic hypertension and employed the protocol of early concomitant vasopressin use, the clinical benefit of the high-MAP strategy was not observed in any outcome or subpopulation.

Participants

Eligible patients were individuals aged ≥ 65 years, clinically diagnosed with septic shock, and admitted to an intensive care unit. Septic shock was diagnosed based on the Sepsis-3 definition [2]. Fluid resuscitation for the diagnosis of septic shock was not based on the uniform approach of "at least 30 mL/kg of a crystalloid solution within 3 h of the diagnosis" [15] but instead left to the clinician's discretion because of recent findings suggesting the harmful effects of excessive fluid, especially in older populations [16, 17]. Patients who had been on vasopressors for ≥ 3 h, including settings before admission, were excluded, as a previous meta-analysis [18] suggested the potential risk of targeting high MAP after 6 h of norepinephrine administration. Details of the exclusion criteria are provided in ESM 1.

Randomisation and masking

The patients were randomly assigned via an online-based system to the high-target group (target MAP = 80–85 mmHg) or the control group (target MAP = 65–70 mmHg) in a 1:1 ratio, using a centralised, computer-generated allocation sequence prepared by a programmer, independent of the conduct of the trial. Stratified block randomisation was performed according to the presence or absence of a history of chronic hypertension and age (< 80 years or older). Chronic hypertension was determined by previous diagnosis or history of antihypertensive medication. The block size was ten which was not disclosed to all study members, to reduce the predictability of the random sequence. Given the pragmatic character of the trial, a history of chronic hypertension for stratification was determined according to the information at enrolment, regardless of the actual morbidity. The treating physicians were not blinded to the assigned groups owing to the nature of the trial. However, the statisticians were masked to the group allocation until all analyses were completed.

Procedures

The target MAP was maintained for 72 h after randomisation or until vasopressors were no longer needed, owing to improved patient conditions. In the

high-target group, the target MAP was changed to 65 mmHg if an adverse event potentially related to vasopressors occurred. The target MAP after 72 h was determined at the physician's discretion. Since invasive intra-arterial blood pressure can only be monitored in intensive care units, considering the generalisability, blood pressure was measured non-invasively on the upper arm in principle.

In this trial, concurrent use of vasopressin from the early stage was protocolised to minimise the potential adverse effects of catecholamine [19, 20]. If a norepinephrine dose of ≥ 0.1 μg/kg/min was needed to achieve the target MAP, vasopressin was initiated, and the dose was increased to 0.04 U/min. If the target MAP was still not achieved, the treating physician could add another vasopressor, increase the norepinephrine dose, or add dobutamine or hydrocortisone. Similarly, the treating physician determined the volume and speed of fluid administration. In principle, physicians were required to follow the latest clinical practice guidelines for the sepsis management [15, 21]. The decision on whether to reduce or discontinue vasopressors, the initial choice of empiric antibacterial agents, the introduction of mechanical ventilation or renal replacement therapy (RRT), and the use of other adjunctive medications was left to the treating physician. The treating physician also determined the type and dose of analgesics and sedatives, in principle, targeting a Richmond Agitation-Sedation Scale [22] score of − 3 to 0.

Outcomes

The primary endpoint was all-cause mortality 90 days after randomisation. The secondary outcomes included all-cause mortality at 28 days; mortality from sepsis; lactate clearance at 24 h; ventilator-free, RRT-free, and catecholamine-free days at 28 days; and safety endpoints. Details of the secondary outcomes described in ESM 1. The cause of death was judged by the treating physician according to the patient's clinical course. The lactate clearance at 24 h was defined by "100 × (lactate level after the 24 h of ICU admission − lactate level at ICU admission)/lactate level at ICU admission". Support-free days at 28 days of patients who died within 28 days were treated as zero. Major adverse kidney events (MAKE) [23] at hospital discharge were also collected retrospectively.

Statistical analyses

The estimated incidence of the primary endpoint in the control group was 45% based on the previous studies involving a similar population. The anticipated absolute difference from the intervention was 10%. Thus, an estimated 376 patients per group were required to have an 80% power to achieve a two-sided alpha level of 0.05. Assuming that approximately 10% of the patients dropped out for any reason, this trial planned to enrol 836 patients. All analyses were performed by statisticians who were independent of the trial implementation and masked to patient allocation based on a prespecified statistical analysis plan (ESM 2).

The intention-to-treat population was examined in the primary analysis based on randomisation results. A secondary per-protocol analysis was performed on participants who received any treatment for the disease without deviation until the end of the intervention or withdrawal from the trial. Differences in 90-day mortality were compared using Fisher exact test. Secondary analyses included logistic regression adjusted for the factors used for the stratification at registration and survival time analysis by estimating Kaplan–Meier curves, the log-rank test, and other methods. The same analyses were performed for the secondary endpoints of mortality and the incidence of adverse events. A safety analysis was conducted on participants who received any treatment for the disease, regardless of withdrawal from the trial. For the endpoints of lactate clearance and each organ support-free days, summary statistics were compared using the Student's t test, Wilcoxon rank sum test, and other methods, as appropriate. Post-hoc sensitivity analysis using a multivariate logistic regression model was performed to adjust for potential imbalances in the patient background between the trial arms.

Interim analysis was conducted after confirming the 90-day survival outcomes of the 300 patients. Participant registration continued during the interim analysis. Bayesian predictive power was calculated when the planned number of patients was registered. When it declined by approximately ≤ 5%, the safety monitoring board recommended trial discontinuation. As no decision on continuation owing to efficacy was made, the significance level was not adjusted for in the final analysis. Statistical significance was set at a P value of < 0.05. Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

The interim analysis results indicated that the high-target MAP strategy met the predefined termination criteria for ineffectiveness and even suggested harm; therefore, the Safety Monitoring Committee recommended early trial termination, and patient enrolment was discontinued on 12 December 2023. It took approximately eight months from the enrolment of the 300th participant to the interim analysis due to delays in data entry and validation. Finally, between 1 July 2021 and 12 December 2023 among the 561 patients were screened, and 518 were allocated to the high-target (258 patients) and

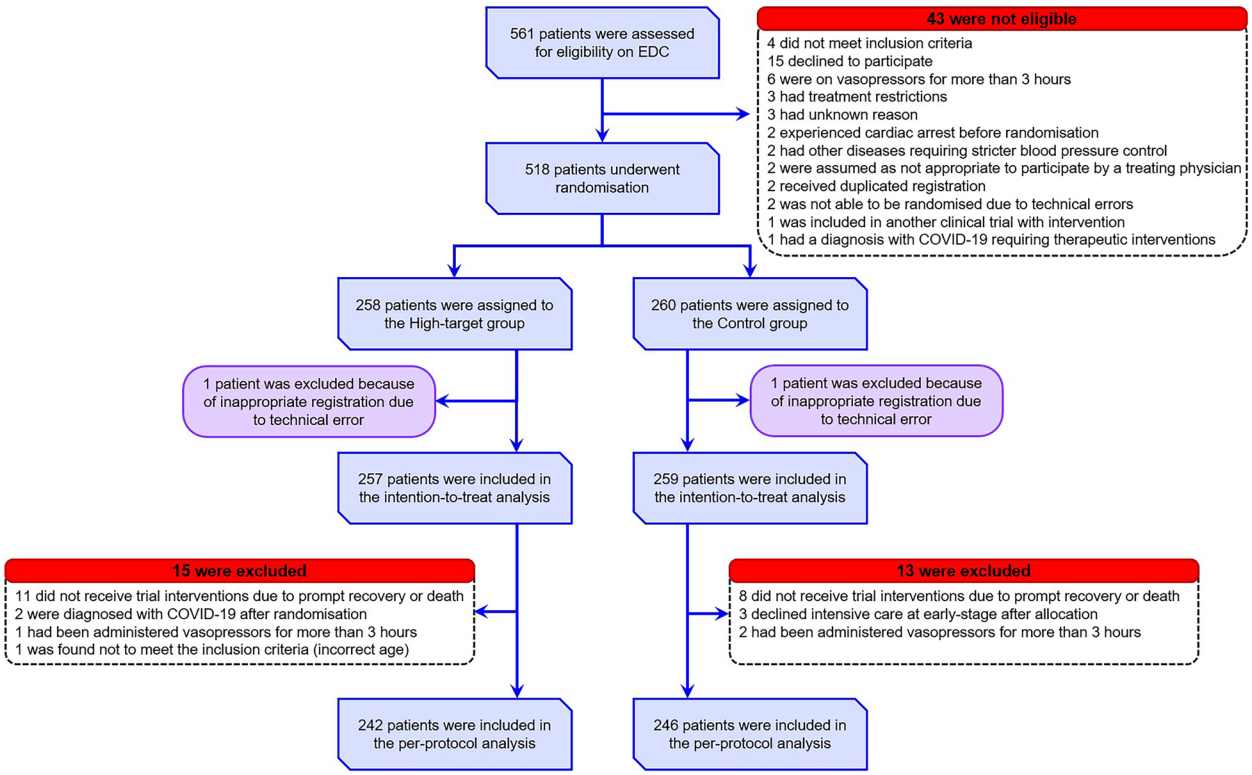
561 patients were assessed for eligibility on EDC
43 were not eligible
4 did not meet inclusion criteria
15 declined to participate
6 were on vasopressors for more than 3 hours
3 had treatment restrictions
3 had unknown reason
2 experienced cardiac arrest before randomisation
2 had other diseases requiring stricter blood pressure control
2 were assumed as not appropriate to participate by a treating physician
2 received duplicated registration
2 was not able to be randomised due to technical errors
1 was included in another clinical trial with intervention
1 had a diagnosis with COVID-19 requiring therapeutic interventions
518 patients underwent randomisation
258 patients were assigned to the High-target group
260 patients were assigned to the Control group
1 patient was excluded because of inappropriate registration due to technical error
1 patient was excluded because of inappropriate registration due to technical error
257 patients were included in the intention-to-treat analysis
259 patients were included in the intention-to-treat analysis
15 were excluded
11 did not receive trial interventions due to prompt recovery or death
2 were diagnosed with COVID-19 after randomisation
1 had been administered vasopressors for more than 3 hours
1 was found not to meet the inclusion criteria (incorrect age)
13 were excluded
8 did not receive trial interventions due to prompt recovery or death
3 declined intensive care at early-stage after allocation
2 had been administered vasopressors for more than 3 hours
242 patients were included in the per-protocol analysis
246 patients were included in the per-protocol analysis

Fig. 1 Patient flow diagram. Patients aged ≥ 65 years who were clinically diagnosed with septic shock based on the Sepsis-3 criteria were assessed for eligibility. A total of 518 patients were randomly assigned to the high-target or control group in a 1:1 ratio. One patient from each group was excluded from the primary analysis because of inappropriate registration owing to technical errors. *EDC* electronic data capture, *MAP* mean arterial pressure

control (260 patients) groups (Fig. 1). After excluding two patients with registration errors (one from each group), 516 patients were included in the analysis. All participants were Japanese. The median age (interquartile range) of the overall population was 78 years (73–85). The most common source of infection was the abdomen (30.2%), followed by the urinary tract (26.4%) and lungs (25.0%). The median duration from the start of norepinephrine administration to randomisation was 60 min in both groups. The baseline characteristics were similar between the two groups (Table 1; ESM 3, Table E1). Approximately 53.3% of the high-target group and 52.9% of the control group had a history of chronic hypertension.

MAP during and after resuscitation was significantly higher in the high-target group than in the control group in the first 64 h (Fig. 2; ESM 3, Table E2–E3 and Figure E1). The median time to reach the target MAP (interquartile range) for the first time was 3 h (1–7) in the high-target group and 1 h (0–3) in the control group. Sixteen patients in the high-target group and five patients in the control group died before reaching the target MAP. The median vasopressor administration period in the high-target and the control groups was 65 h and 42 h, respectively (Fig. 2; ESM, Table E4). The target MAP was reduced to 65–70 mmHg in two patients in the high-target group due to adverse events. Clinical management during the 72 h after randomisation is summarised in Table E5 in ESM 3. The administered fluid volume was similar between the arms. The median norepinephrine doses used during the first 72 h were 15.6 mg in the high-target group and 9.6 mg in the control group, and those for vasopressin were 34.0 U and 11.8 U, respectively. Corticosteroid supplementation was performed in 60.3% of the patients in the high-target group and in 56.8% of those in the control group.

By 90 days after randomisation, 101 patients (39.3%) in the high-target group and 74 patients (28.6%) in the control group had died from any cause (risk difference = 10.7; 95% CI, 2.6 to 18.9) (Table 2). There were no differences between two groups regarding causes of death other than primary sepsis, including the death due to ischemic events (ESM, Table E6). The cumulative number of patients who had died within 90 days is shown in Fig. 3. Death due to sepsis within 90 days of randomisation occurred in 77 patients (30.0%)

in the high-target group and 46 patients (17.8%) in the control group (risk difference = 12.2; 95% CI, 4.9 to 19.5). Cumulative number of deaths according to the cause of death is shown in Figure E2 in ESM 3. The mean RRT-free days at 28 days (standard deviation) were 18 (13.1) days in the high-target group and 20 (12.1) days in the control group (difference = 2.5 days; 95% CI − 4.7 to − 0.3). All main safety outcomes occurred more frequently in the high target group, including arrhythmia, thromboembolism, ischaemia not caused by thromboembolism, and haemorrhagic events requiring blood transfusion.

The sensitivity analysis using a Wilcoxon rank sum test demonstrated similar results (ESM, Table E7). No clinical benefit of the high-MAP strategy was observed for any outcomes in any subpopulation, including patients with known chronic hypertension (ESM 3, Table E8 and Figures E3–E4). The secondary per-protocol analyses and the prespecified sensitivity analysis adjusted by the stratification factors demonstrated similar results (ESM 3, Tables E9–E10 and Figure E5). The results of the post-hoc multivariate analysis adjusted for potential confounders were similar to those of the primary analysis (ESM 3, Table E11).

Table 1 Patient baseline characteristics (intention-to-treat population)

	High-target group (*N* = 257)	Control group (*N* = 259)
Median age (IQR)—yr	79 (74–84)	77 (73–85)
Male sex—no. (%)	143 (55.6)	137 (52.9)
Japanese ethnicity—no. (%)	251 (97.7)	255 (98.5)
Median body mass index (IQR)	21.2 (18.6–24.3)	21.5 (18.3–24.6)
Median clinical frailty scale (IQR)	5 (3–6)	4 (3–6)
Transfer from another hospital—no. (%)	59 (23.0)	69 (26.6)
In-hospital onset—no. (%)	47 (18.3)	37 (14.3)
Comorbidities—no. (%)		
Chronic hypertension	137 (53.3)	137 (52.9)
Ischaemic heart disease	29 (11.3)	24 (9.3)
Chronic heart failure	46 (17.9)	43 (16.6)
Chronic obstructive pulmonary disease	12 (4.7)	10 (3.9)
Chronic kidney disease	41 (16.0)	37 (14.3)
Liver cirrhosis	5 (1.9)	6 (2.3)
Diabetes mellitus	66 (25.7)	74 (28.6)
Cancer	43 (16.7)	33 (12.7)
None	42 (16.3)	63 (24.3)
Source of infection—no. (%)		
Lung	65 (25.3)	64 (24.7)
Abdomen	80 (31.1)	76 (29.3)
Urinary tract	61 (23.7)	75 (29.0)
Soft tissue	21 (8.2)	27 (10.4)
Blood	9 (3.5)	8 (3.1)
Nervous system	2 (0.8)	0 (0)
Other	1 (0.4)	4 (1.5)
Unknown	23 (8.9)	12 (4.6)
Median mean blood pressure (IQR) at randomisation—mmHg	58 (53–65)	56 (50–64)
Median lactate level (IQR) at randomisation—mmol/L	4.0 (2.7–6.3)	3.9 (2.5–7.0)
Median P/F ratio (IQR) at randomisation	241 (152–352)	265 (160–385)
Median SOFA score (IQR) at randomisation	10 (8–12)	9 (7–12)
Median APACHEII score (IQR) at randomisation	27 (21–32)	25 (20–32)
Median duration (IQR) from the start of norepinephrine administration to randomisation—min	60 (20–120)	60 (15–107)

Summary statistics were calculated excluding missing values. The numbers and proportions of missing values for each variable are described in Table E1

IQR interquartile range, *P/F ratio* the ratio of partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspiratory oxygen concentration (FiO_2), *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology Assessment and Chronic Health Evaluation

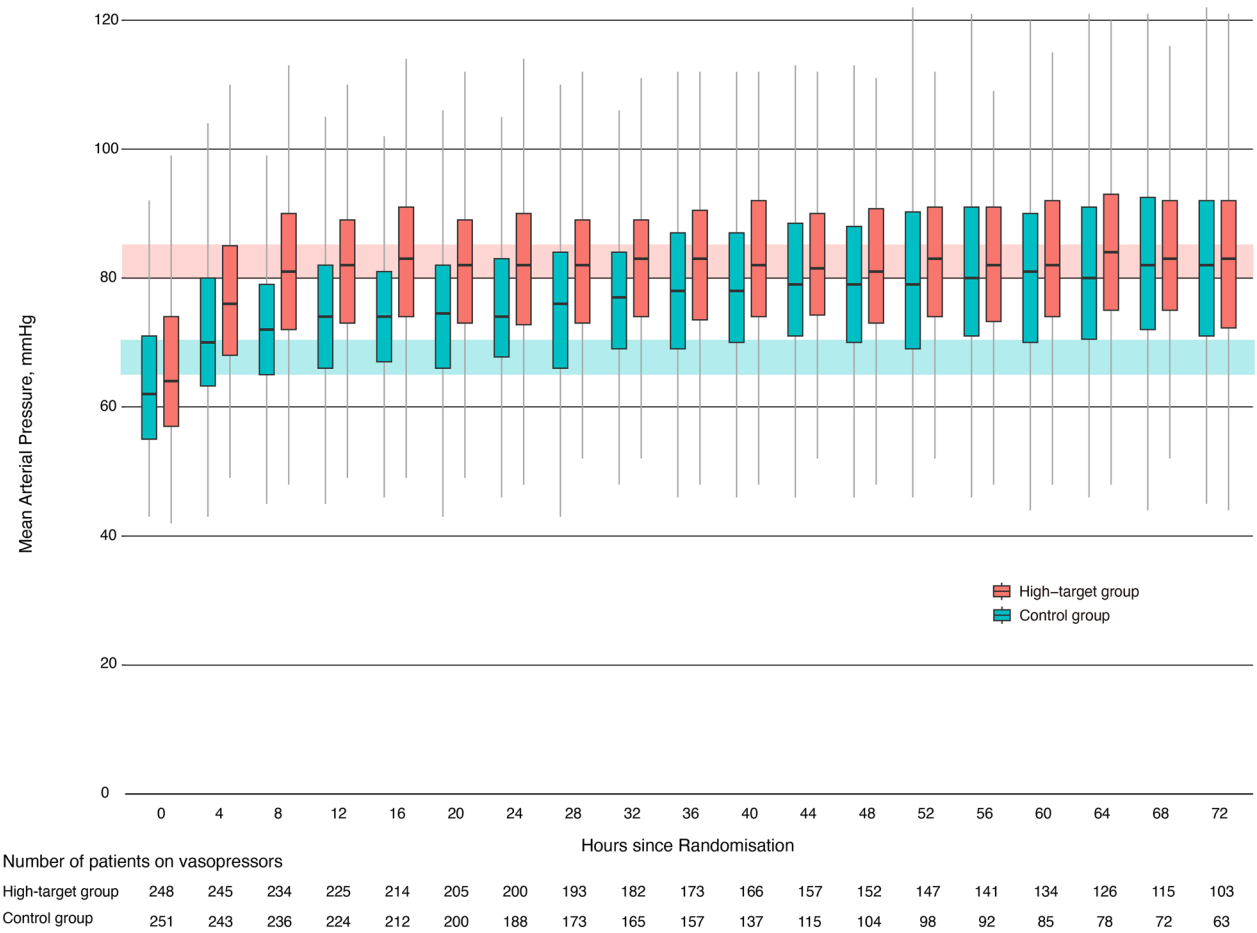

Fig. 2 Blood pressure management according to mean arterial pressure target. The box and whisker plots show transition of median MAPs and interquartile ranges according to the target MAP. The red shaded region shows the target range of the high-MAP group, while blue shaded region shows the target range of the control group. Outliers are not shown. The target MAP was achieved 8 h after randomisation in majority of patients in the high-target group and 4 h after randomisation in the control group. Number of patients receiving vasopressors is also shown. The median vasopressor administration period in the high-target group and the control group was 65 h and 42 h, respectively. *MAP* mean arterial pressure

Discussion

The OPTPRESS trial examined the effectiveness of high-target MAP in patients aged ≥ 65 years with septic shock in Japan. In addition, this trial used the strategy of early use of vasopressin, which has been proposed as a novel approach in recent years [19, 20], to minimise the adverse effects related to catecholamines. As a result, targeting a MAP of 80–85 mmHg significantly increased mortality compared with management targeting a MAP of 65–70 mmHg. All secondary outcomes regarding survival and organ support-free days were significantly lower in the high-target group. Potential effect modifiers, including chronic hypertension, had little effect on the outcomes. While cumulative evidence from Western countries suggested the futility of a higher MAP strategy in vasodilatory shock in general [4–7, 24], the generalisability has been limited because patterns of diseases that have a significant impact on systemic haemodynamics, including cardio and cerebrovascular diseases, vary depending on country, region, and ethnicity [25]. This trial could have added global relevance to the existing evidence on this topic by conducting trials in underrepresented regions.

Consistent with previous trials [4–6], the actual MAP in the control group exceeded the target range. Since more than half of patients no longer did not receive vasopressors after 42 h of randomization in the control group, it was considered that the excess was largely led by improved patient condition, not by the issue of protocol compliance. Meanwhile, some patients could not reach the target MAP even with high-dose vasopressor because of their poor condition. This difference in target

Table 2 Clinical outcomes (intention-to-treat population)

	High-target group (N = 257)	Control group (N = 259)	Difference (95% CI)	*P* value
Primary outcome				
All-cause mortality at 90 days—no. (%)	101 (39.3)	74 (28.6)	10.7 (2.6 to 18.9)**	0.012*
Secondary outcomes				
All-cause mortality at 28 days—no. (%)	78 (30.4)	56 (21.6)	8.7 (1.2 to 16.3)**	0.027*
Mortality from sepsis at 90 days—no. (%)	77 (30.0)	46 (17.8)	12.2 (4.9 to 19.5)**	0.001*
Mortality from sepsis at 28 days—no. (%)	62 (24.1)	42 (16.2)	7.9 (1.0 to 14.8)**	0.028*
Mean renal replacement therapy-free days at 28 days (SD)—days	18 (13)	20 (12)	− 2.5 (− 4.7 to − 0.3)††	0.024†
Mean ventilator-free days at 28 days (SD)—days	15 (12)	18 (12)	− 2.7 (− 4.8 to − 0.6)††	0.012†
Mean catecholamine-free days at 28 days (SD)—days	16 (11)	19 (10)	− 2.4 (− 4.3 to − 0.5)††	0.012†
Mean lactate clearance at 24 h (SD)—%‡	31.4 (74.2)	39.7 (44.6)	− 8.4 (− 19.5 to 2.8)††	0.140†
Mean change in clinical frailty scale at 90 days (SD)§	1 (2)	1 (2)	− 0.2 (− 0.5 to 0.2)††	0.355†
Major kidney adverse events at hospital discharge¶—no. (%)	94 (37.8)	79 (31.5)	6.3 (− 2.0 to 14.6)**	0.158*
Safety outcomes‖				
Any arrhythmia—no. (%)	34 (13.2)	29 (11.2)	2.0 (− 3.6 to 7.7)**	0.504*
Ischaemic events—no. (%)	23 (9.0)	14 (5.4)	3.5 (− 0.9 to 8.0)**	0.128*
Haemorrhagic events—no. (%)	14 (5.5)	8 (3.1)	2.4 (− 1.1 to 5.8)**	0.199*

CI confidence interval, *SD* standard deviation

**P* values were calculated using the Fisher exact test

***Risk difference is provided

† *P* values were calculated using Student's *t* test

†† Mean difference is provided

‡ Summary statistics were calculated based on 228 and 234 patients in the high-target group and the control group, respectively

§ Summary statistics were calculated based on 192 and 161 patients in the high-target group and the control group, respectively

¶ Major adverse kidney events include any of persistent kidney dysfunction defined by a ≥ 25% decline in eGFR from the reference, continued need for RRT, and death. This outcome was not defined a priori and collected retrospectively. Summary statistics were calculated based on 249 and 251 patients in the high-target group and the control group, respectively

‖ Summary statistics were calculated in the safety analysis population in which at least one treatment intervention (fluid administration, norepinephrine use, vasopressin use, or epinephrine use) was provided. The safety analysis population included 247 and 251 patients in the high-target and the control groups, respectively

and observed MAP is the reason why this topic can be appropriately examined only in randomized trials rather than analysis of existing observed data. Although the difference in MAP between the groups was smaller than trial protocol, clear separation in MAP between the arms from 8 h of randomisation means that it is reasonable to compare the effect.

In this trial, while the administered fluid volume was similar between the arms, the cumulative amount of vasopressors was higher in the high-target group. As suggested in a previous prospective study [26], the vasopressor-related risks might have outweighed the hypotension-related risks in the high-target MAP strategy with increased exposure to vasopressors. Theoretically, there is a risk of organ ischemia due to excessive vasoconstriction [27]. Increased risk of various comorbidities in older population may make them more vulnerable to vasopressors-induced adverse events. However, although adverse events were more frequent in the high-target group, there were no differences in causes of death other than sepsis, including the death due to ischemic events, between the arms (ESM 3, Table E6 and Figure E2). It was reported that vasopressors have immune effects potentially influencing the outcome of septic shock. Norepinephrine is suggested to have immunosuppressive and bacterial growth-promoting effects in preclinical models [28, 29]. Contrary to a previous trial [4] that suggested the benefits of a high MAP target for renal function in patients with chronic hypertension, such a trend was not observed regarding MAKE development and RRT-free days. The difference in baseline conditions, including age and prevalence of chronic kidney disease, might have caused these differences. Another trial that included patients aged ≥ 65 years and compared the effect of target MAP reported no difference in renal replacement days [6].

Recently, personalised resuscitation was proposed [30, 31]. A randomised trial [32] reported reduced postoperative organ dysfunction following personalised blood pressure management during general anaesthesia. However,

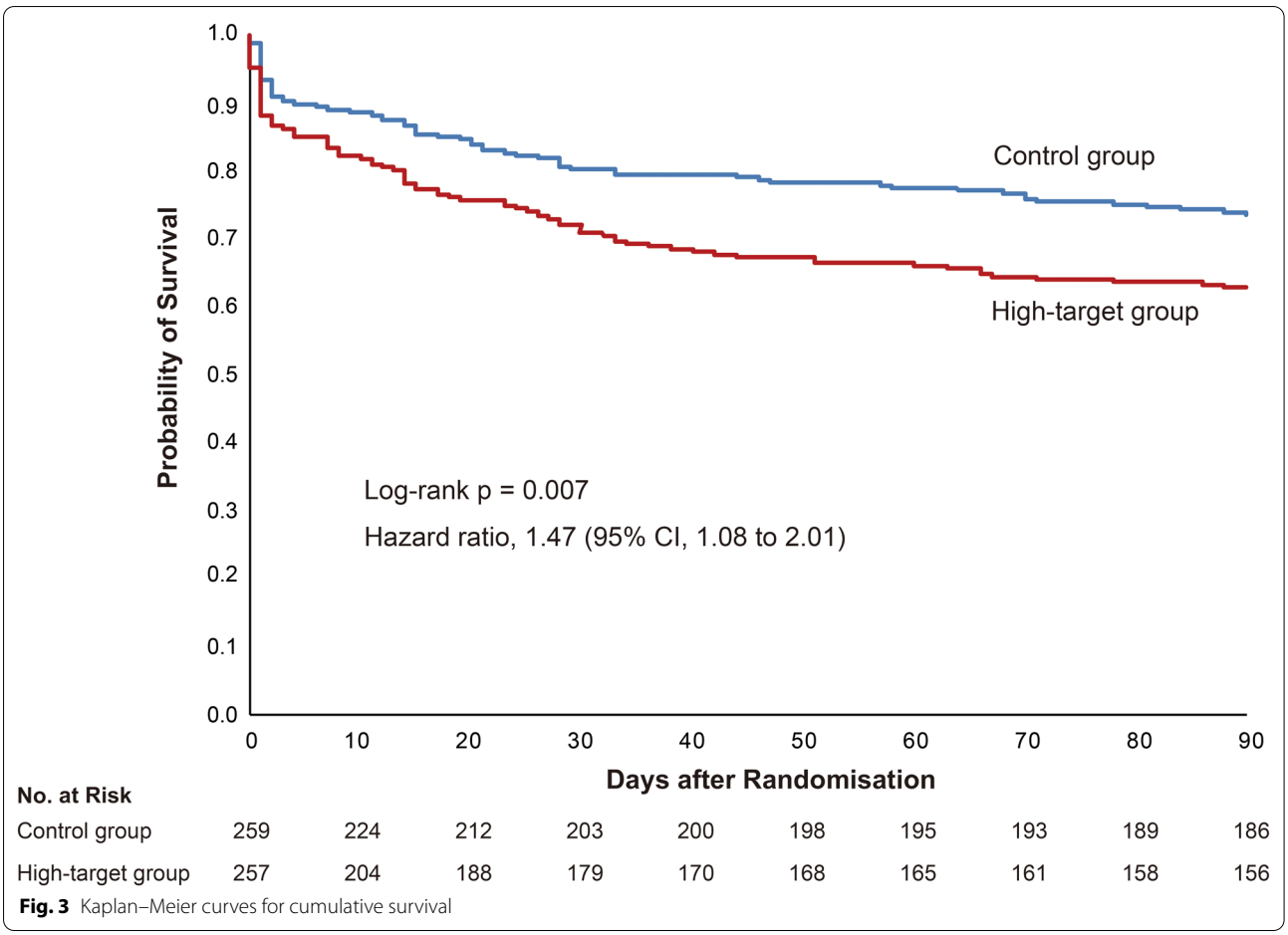

Fig. 3 Kaplan–Meier curves for cumulative survival

information on blood pressure before illness onset is not always available in emergency settings, and undiagnosed chronic hypertension is common [33]. Additionally, the effectiveness of fluid resuscitation and vasoactive agents depends on pre-existing cardiovascular conditions and cardiac depression due to sepsis. Cardiac function monitoring and management were not protocolised in this trial, regardless of pre-existing cardiac conditions. The effectiveness of personalised haemodynamic management, considering a patient's cardiovascular status, using echocardiography or haemodynamic monitoring devices, should be evaluated in the future.

The present trial has some limitations. The open-label design might have affected the clinical management and have introduced bias such as outcome ascertainment. The use of fixed blocks could have led ineffective randomisation concealment. The status of chronic hypertension comorbidity was sometimes incorrect, owing to limited information on emergency settings and undiagnosed status. There was no strict titration or tapering protocol for vasopressors, which might had led to differences in the period to reach target MAP and the accuracy of MAP control. The pre-estimated mortality rate to calculate sample size was higher than observed mortality rate. While pre-estimation was made based on data from Europe and the United States given the scale of the study, previous epidemiological study suggested different mortality rates in sepsis between Western countries and Japan [34, 35]. Since information on the non-serious adverse events were not reported immediately, concern of under reporting existed. In addition, records of adverse events on detailed time of occurrence and onset after 72 h were lacked. While the result of this trial could provide insights from a previously unexplored region, generalisability was limited due to the nature of single-country trial and ethnic homogeneity.

Conclusions

Among older patients with septic shock in Japan, despite the use of a catecholamine-sparing protocol with vasopressin, management targeting a MAP of 80–85 mmHg did not reduce and instead significantly increased mortality compared with management targeting a MAP of 65–70 mmHg. It would be reasonable to be attentive to

excessive vasopressor use in patients with septic shock unless novel evidence emerges in the future.

Supplementary Information
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Author contributions
All authors contributed to the trial design, interpretation of data, and critical revision of the final version of the report. AE acquired funding for this trial. AT and KT contributed to the statistical design and analysis. AE, KY, TT, and YU wrote the first draft of this manuscript. All authors had the opportunity to provide input into the study protocol, access the data in the study, and have the final responsibility for the decision to submit for publication. The corresponding author confirms that all listed authors meet the authorship criteria and that none meeting the criteria have been omitted.

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Data availability
After all ancillary analyses by the trial group, the datasets analysed in the present study will be available from the corresponding author on reasonable request and after the approval of the Steering Committee members.

Declarations

Conflicts of interest
The authors declare no conflicts of interest that could influence or bias the implementation and results of this study.

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